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Title: Twin anemia polycythemia sequence  
Issue Date: 2014-10-28
General introduction
Figure 1. Dizygotic twins versus monozygotic twins resulting in dichorionic and monochorionic twins
General Introduction

Twin pregnancies are at increased risk for adverse outcome compared to singletons. The incidence of twin pregnancies in the Netherlands is approximately 2% [1], of which 1/3 are monozygotic (identical) twins and 2/3 dizygotic (non-identical) twins. Dizygotic twin pregnancies are always dichorionic and each fetus has thus its own placenta. In 1/3 of monozygotic twin pregnancies, dividing into two embryos occurs within three days after fertilization resulting also in a dichorionic twin pregnancy. In 2/3 of monozygotic twins, dividing occurs after three days resulting in monochorionic twins, with both fetuses sharing their placenta. Dividing after 8 days results in monoamniotic twins, besides sharing the placenta these twins also share the amniotic sac (figure 1). With a total of approximately 175,000 pregnancies per year in the Netherlands, approximately 775 twin pregnancies are monochorionic.

Monochorionic twins share their placenta and their blood circulation is connected by vascular anastomoses at the placental surface. In monochorionic placentas three types of anastomoses are seen: artery to artery, vein to vein and artery to vein. An arterio-venous (AV) anastomosis is a “deep hidden” anastomosis. The artery of one twin is corresponding with a vein of the co-twin via a shared cotyledon. Blood flow goes in one direction from artery to vein and therefore unidirectional. Artery to artery (AA) and vein to vein (VV) anastomoses are “superficial” anastomoses since they lie on the placental surface and these anastomoses are bi-directional. In contrast, dichorionic placentas almost never have vascular anastomoses and the circulations of both fetuses are not connected. Dichorionic placentas have a thick intertwin membrane. Figure 2 shows the placenta and ultrasound differences in monochorionic versus dichorionic twins.

Monochorionic twin pregnancies are associated with a perinatal mortality rate of 11% [2;3]. Due to imbalanced blood flow through placental vascular anastomoses, these pregnancies can be complicated by twin-twin transfusion syndrome (TTTS) or twin anemia polycythemia sequence (TAPS).

TTTS

TTTS is caused by an imbalanced blood flow from donor to recipient via placental vascular anastomoses, resulting in hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient twin. The incidence of TTTS is approximately 10% [3]. If left untreated, TTTS can result in an overall mortality rate of 73-100% [4]. In the
Figure 2. Monochorionic (left) versus dichorionic (right).

In the middle the ultrasound image shows a T-sign in monochorionic twins and a lambda sign for dichorionic twins.

At the bottom placentas after color dye injection are shown. Arteries are injected with green and blue dye and veins with yellow and pink.

A monochorionic placenta is characterized by vascular anastomoses at the placental surface whereas a dichorionic placenta has a thick intertwin membrane and no vascular anastomoses.

Figure 3. Twin twin transfusion syndrome (TTTS). D is the donor and R is the recipient.

polyhydramnios
hypervolemia
polyuria
oligohydramnios
oliguria
hypovolemia
Netherlands, of the approximately 775 monochorionic pregnancies a total of 70 to 80 pregnancies are complicated by TTTS[1]. The preferred treatment option for TTTS is fetoscopic laser coagulation of the vascular anastomoses at the placental surface. The Leiden University Medical Center (LUMC) is the national referral center for fetal therapy, a total of up to 60 patients are treated annually with fetoscopic laser surgery for TTTS.

**TAPS**

TAPS is a newly described form of chronic feto-fetal transfusion in monochorionic twins. TAPS is characterized by large intertwin hemoglobin (Hb) difference without amniotic fluid differences as in TTTS. TAPS was first described in 2005 by Robyr et al. [5] as a complication after fetoscopic laser surgery for TTTS. In 2007 Lopriore et al. [6] named this complication in monochorionic twins: twin anemia polycythemia sequence, TAPS. Since then TAPS is worldwide accepted as a name for this complication in monochorionic twins. TAPS may occur spontaneous or after laser treatment for TTTS (post-laser TAPS). The incidence of spontaneous TAPS varies between 1-5% [3;7-9] and the incidence of post-laser TAPS is 13% [5]. In the Netherlands up to 40 pregnancies are complicated by spontaneous TAPS and around 8 pregnancies by post-laser TAPS per year.

**Solomon study**

Post-laser TAPS is caused by residual anastomoses after fetoscopic laser surgery for the treatment of TTTS. In up to 33% after fetoscopic laser surgery for TTTS residual anastomoses are seen [5;10;11]. In order to reduce the number of residual anastomoses, a new laser technique, named the Solomon technique is studied (chapter 7). In the Solomon trial (Selective Or Laser Of the entire equator in MONochorionic twins) we compare the Solomon technique with the standard technique. With the Solomon technique, after identification and coagulation of the individual anastomoses, the whole vascular equator will be coagulated and with the standard technique only the anastomoses will be coagulated. Solomon also refers to the bibilq story of King Solomon. King Solomon was the son of David, and reigned from 970 to 931 BC. He was known for his wisdom. In one account, known as the Judgment of Solomon, two women came before Solomon to resolve a quarrel over whom was the true mother of a baby. When Solomon suggested they should divide the living child in two with a sword, one woman said she would rather give up the child than see it killed. Solomon then declared the woman who showed compassion to be the true mother, and gave the baby to her. In our trial, instead of cutting one baby in two to give two mothers half a baby, we aim to “cut” the placenta in two, to give one mother two babies.
The aim of this thesis is to improve our knowledge on this newly described chronic form of feto-fetal transfusion in monochorionic twins. Improving our knowledge on TAPS is of utmost importance to diagnose, manage and treat this complication in a pregnancy with an increased risk of perinatal mortality and morbidity. Several questions were raised considering pathophysiology, diagnosis, treatment, neonatal and long-term outcome.

**Pathophysiology**
To understand the pathophysiology of TAPS we studied the placentas from TAPS pregnancies and compared these with placentas of uncomplicated monochorionic twin pregnancies and placentas after fetoscopic laser surgery for TTTS. We formulated the following questions: What are the type and size of anastomoses in TAPS compared to uncomplicated monochorionic twin pregnancies and in placenta after fetoscopic laser surgery for TTTS? Is there a difference in spontaneous TAPS and post-laser TAPS placentas?

**Diagnosis**
Timely and accurate diagnosis is important for perinatal outcome. Since there is not an...
obvious sign as amniotic fluid difference as in TTTS, TAPS can easily be missed in less experienced hands. When TAPS is not timely diagnosed it may result in perinatal mortality or severe morbidity. Middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurements is proven to be an accurate non-invasive predictor for anemia in red cell alloimmunization [12]. Is MCA-PSV measurement also an accurate predictor of anemia and polycythemia in TAPS? And in postnatal TAPS what are the hematological characteristics in donors and recipients?

Treatment
The best treatment for TTTS is fetoscopic laser surgery of the vascular anastomoses, which is a causal treatment for this form of feto-fetal transfusion [13]. The best treatment option for

Figure 5. Twin anemia polycythemia sequence (TAPS). The pale donor is anemic and the plethoric recipient is polycythemic, without amniotic fluid differences.
TAPS is not known. How should we manage this form of feto-fetal transfusion? Is there a role for fetoscopic laser surgery? If laser is not feasible and intrauterine transfusion is performed should we add partial exchange transfusion for the recipient? Even more important, can we prevent post-laser TAPS with the Solomon technique?

Figure 6. Solomon versus standard technique
Neonatal and long-term outcome

For optimal neonatal care diagnostic criteria for postnatal TAPS and the risk associated with this complication in monochorionic twins should be known. How can we diagnose TAPS postnatally and what should be the criteria? What are the hematological and biochemical characteristics in TAPS donors and recipients? Is TAPS limited to hematological complications? What is the long-term neurodevelopmental outcome in TAPS? And can we identify risk factors for impaired neurodevelopmental outcome?

This thesis will provide answers to the above-mentioned questions and provides diagnostic tools, a stage based classification system, treatment options, how to prevent post-laser TAPS and information on neonatal outcome.

Outline of this thesis

Part I. General introduction

Part II. Review

Chapter 1 – Review of the literature on TAPS. This review focuses on the pathogenesis, incidence, diagnostic criteria, management options and outcome in TAPS. In this review we also proposed a classification system for antenatal and postnatal TAPS.

Part III. Pathogenesis

Chapter 2 – Study on placentas with residual anastomoses after fetoscopic laser surgery for TTTS. Localization, size and consequences of residual anastomoses were studied in this chapter.

Chapter 3 – Study on placenta characteristics in spontaneous versus post-laser TAPS. Localization, size, type, and number of anastomoses were compared between spontaneous TAPS placentas and post-laser TAPS placentas.

Chapter 4 – Study on AA anastomoses in spontaneous TAPS placentas compared to uncomplicated monochorionic twin placentas.
Part IV. Diagnosis

Chapter 5 – This is the first study on MCA-PSV measurements in TAPS. We studied the correlation between MCA-PSV measurements and Hb-deficit.

Chapter 6 – Study on hematological characteristics in neonates with TAPS. In this study we also proposed diagnostic criteria for postnatal detected TAPS.

Part V. Antenatal management and outcome

Chapter 7 – A randomized controlled trial (Solomon trial) on fetoscopic laser surgery for TTTS. We compared the standard selective technique, where only anastomoses were coagulated, with the Solomon technique, where the whole vascular equator was coagulated. We hypothesized that with the Solomon technique the amount of residual anastomoses will be reduced and therefore highly important for the prevention of post-laser TAPS.

Chapter 8 – In this study we reported the secondary outcome of the Solomon trial. We examined and analyzed all placentas that were injected with color dye within the Solomon trial.

Chapter 9 - In this model simulation we show that the addition of PET to IUT, reduces the severity of polycythemia and possible complications as a consequence of hyperviscosity in the recipient.

Chapter 10 – Study on the management options in antenatal detected TAPS. Laser surgery for TAPS appears to improve perinatal survival and neonatal outcome compared to expectant management and intrauterine transfusion.

Part VI. Postnatal management and outcome

Chapter 11 – In this study we compare levels of albumin and total protein in TAPS donors and TAPS recipients. Additionally we looked at placental share in correlation to birth weight.

Chapter 12 – In this case report we showed a case with severe cerebral injury
after post-laser TAPS resulting in neonatal death. This case report shows that TAPS is more than large intertwin Hb difference and also highlights the importance of antenatal Doppler ultrasound monitoring and choice of management.

**Chapter 13** – Study on long-term neurodevelopmental outcome in post-laser TAPS. Risk factors were assessed and a subgroup analysis was performed on low cognitive scores.

*Part VII. Summary and general discussion*

In the summary and general discussion the most important findings of this thesis is outlined and future perspectives are given.
References